II. REMARKS

A. Status of the Claims

Claims 1-51 were pending in the case at the time of the Office Action. The Action indicates that claims 5, 30, and 38-51 are withdrawn from consideration because they are not directed to the elected species of "growth factor." Applicant notes, however, that claims 5, 30, 40 and 47 recite "nerve growth factor," and should thus not be withdrawn since they read on the elected species of "growth factor." Claims 1, 11, 24, 36, and 37 have been amended in the Amendment set forth herein. Claims 2-3, 12-23, and 25-26 have been canceled without prejudice or disclaimer. No new claims have been added. Support for the amendments of the claims can be found generally throughout the specification, such as in the claims as originally filed and on page 11, line 24 – page 12, line 6; page 5, lines 12-23; page 6, lines 1-11; and page 9, lines 18-20. Thus, claims 1, 4-11, 24, 27-37, 40, and 47 are currently under consideration and presented for reconsideration.

B. The Enablement Rejections Under 35 U.S.C. §112, First Paragraph, Are Overcome

Claims 1-5, 6-11, 24-29, and 31-37 are rejected under 35 U.S.C. §112, first paragraph, because the specification is said to not be enabling for the full scope of the claims. The Examiner argues that while the specification is enabling for methods and processes for increasing the circulating level of a self protein that is erythropoietin or a growth hormone that undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*, it is said to not be enabling for the full scope of the claims. Applicant respectfully traverses.

The Examiner appears to argue that because the instant specification does not teach a use of the invention other than for gene therapy, that the claims are not enabled for such other

applications by the instant specification. Without conceding that the claims are not enabled for non-therapeutic applications, Applicant notes that the claims have been amended to pertain to processes "for treating an immunocompetent human with a hormone deficiency ..." Claims 1 and 24. Therefore, to the extent that the enablement rejection is based on subject matter concerning non-therapeutic applications, that part of the rejection has been overcome. Written description for the amendments to the claims is as discussed above.

The Examiner next proceeds to argue that the specification does not adequately teach how to use the claimed methods in gene therapy applications. Applicant notes that the specification provides substantial and detailed information regarding the claimed processes of treating a hormone deficiency. Information regarding proteins present in the circulation of an animal can be found, for example, on page 4, lines 8-18. Information regarding viral vectors that can be applied in the context of the present invention can be found, for example, on page 5, lines 3 – page 8, line 25 and page 10, line 3 – page 11, line 14. Information regarding *in vivo* and *ex vivo* transformation of muscle cells can be found generally throughout the specification, such as on page 11, line 15 – page 12, line 7. Detailed information regarding processes for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal that involve delivery of viral vectors *in vivo* to muscle cells can be found throughout the specification, such as in working Examples 5-10 (page 16, line 11 - page 23, line 6). Further, the information pertaining to use of plasmid vectors set forth in Examples 1-4 of the specification provides additional detail that can be applied by one of ordinary skill in the art in the practice of the claimed methods. Further, the data set forth in the specification demonstrates that the processes that are claimed result in stable long-term expression of a self-protein in an immunocompetent subject.

That the specification does not include in its examples any data concerning treatment of an animal with a hormone deficiency is not dispositive as to the question of enablement. Applicant reminds the Examiner that the test of enablement is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. See *Manual of Patent Examining Procedure (MPEP)* §2164.01. In view of the information set forth in the specification as discussed above, a person of ordinary skill in the art would be able to practice the claimed processes without an undue amount of experimentation. No evidence has been set forth by the Examiner to establish undue experimentation in implementing a process on an animal with a hormone deficiency under circumstances as set forth herein where the data is directed to animals without a hormone deficiency.

The Examiner argues that the specification does not provide guidance as to how the claimed processes can be used in the treatment of disease in an animal, and that the specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required, for treatment of any pathological condition. Applicant disagrees. The specification provides detailed guidance to one of ordinary skill in the art regarding treatment of disease. For example, page 6, lines 9-11 clearly indicate that the results set forth in the specification can be safely and effectively applied to treat patients with Epo-responsive anemias. Furthermore, the background section on pages 1-2 of the specification clearly delineates that diseases contemplated for treatment by the present invention include those diseases associated with "inherited and acquired serum protein deficiencies including hemophilia A, diabetes mellitus, and erythropoietin-responsive anemias," to name a few examples.

Specification, page 1, lines 13-16. Applicant is not required to explicitly recite every disease that can be treated using the processes of the present invention. The state of the art pertaining the level of understanding pertaining to diseases associated with protein deficiencies was high at the priority date; no evidence to the contrary has been submitted by the Examiner.

The burden of setting forth a *prima facie* case of unpatentability under 35 U.S.C. §112, first paragraph, is with the Examiner. See *MPEP* §2164.04. The Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. *Id.* Here, the Examiner concedes that the specification is enabling for increasing the circulating levels of erythropoietin but not for other self proteins. No reasonable basis has been set forth to establish that one of ordinary skill in the art would not be able to apply the information set forth in the specification to increasing the circulating level of other hormones, and applying the claimed methods to the treatment of disease.

Regarding the Examiner's assertion that the specification provides insufficient guidance pertaining to the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, the specific guidance in the context of erythropoietin is provided on page 6, lines 1 – page 8, lines 25. Detailed information is set forth in this section regarding dosage of viral vector in animals, and effect of dose modification on serum erythropoietin level and hematocrit. In view of the specific and detailed guidance set forth herein pertaining to erythropoietin, one of ordinary skill in the art would be able to apply this information in a process for increasing the serum level of any other hormone. No reasonable basis to doubt this ability has been set forth by the Examiner. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided by the

claimed invention). To the extent that any experimentation would be involved, no evidence has been set forth to indicate that such experimentation would be undue experimentation.

Here, the Examiner argues that the specification does not provide any guidance as to "the use of the claimed DNA methods to treat a diseased animal" because "[t]he specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required." Office Action, page 4. Regarding the level of gene expression required, the claims are directed to processes and methods for increasing the circulating level of a hormone in the blood stream of an immunocompetent animal. If expression of such gene is not increased, then the process or method falls outside of the scope of the claimed invention. Regarding the question as to how much of an increase in the circulating level of a hormone should be sufficient to treat a disease, Applicant respectfully submits that determining a response to therapy and determining how much of an expression of a gene may be sufficient to result in a therapeutic response falls within the level of ordinary skill of one of ordinary skill in the art. If, for example, an increase in circulating level of a hormone is not sufficient to result in a therapeutic effect, then the clinician of ordinary skill would understand that, for example, a repeat administration of transformed muscle cells may be required. Each of the issues set forth by the Examiner, including when and for how long a gene should be expressed, are questions which are readily addressed by those of ordinary skill in the art. While some assessment may be required to optimize the method to result in a therapeutic effect, no reasonable basis has been set forth by the Examiner to establish that any undue experimentation would be required to optimize dose to result in a therapeutic response.

Applicant disagrees with the Examiner's statement that at the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredicable. Applicant previously submitted a review article published around the time of the priority date (Svensson *et al.*, Molecular Medicine Today, April 1996, pp. 166-172; hereinafter "Svensson"; Exhibit 1 of response to Office Action dated February 13, 2007) which provides as follows:

> **"The past five years have witnessed tremendous growth in the field of gene therapy, with pre-clinical and clinical gene therapy trials for diseases as diverse as cancer, AIDS, and atherosclerosis. These studies have utilized many different vectors and target organs in order to achieve therapeutic effects."**

Svensson proceeds to provide an overview of the state of the art regarding ***muscle-based gene therapy***, including the state of the art pertaining to myoblast transplantation (page 167-168), direct DNA injection (page 168), adenovirus vectors (page 168-169), and other vector systems for muscle based gene therapy (page 169). Furthermore, there was discussion regarding diseases that can be targeted using gene-based therapy (pages 169-170). Thus, contrary to the Examiner's assertion, the state of the art was not so very poorly developed and unpredictable in the field of the invention. It was clearly sufficiently advanced such that a person of ordinary skill in the art, when presented with the information set forth in the specification, would have been able to practice the claimed invention without an undue amount of experimentation.

The Examiner quotes articles including a reference from Theodore Friedmann in Scientific American and Verma in Nature in September 1997 which are alleged to be pessimistic regarding the state of the art of gene therapy. Applicant notes that the Examiner has not provided copies of these references or full citations. The quotes that the Examiner refers to in describing pessimism in the field of gene therapy are not indicative of enablement in the state of

the art pertaining to muscle-based gene therapy. The references cited by the Examiner do not indicate that one of ordinary skill in the art would not be able to apply a method to increase the circulating level of a hormone to treat a hormone deficiency. At most, the quotes cited by the Examiner on pages 5-6 of the Office Action merely suggest that continued effort should continue to improve gene therapy technology.

The Examiner also cites to Rubanyi et al. (2001) (copy provided by Examiner) which is alleged to teach technical barriers to gene therapy. Rubanyi *et al.* is a review article which generally discusses the progress which has been made in gene therapy. It does not appear to include any discussion concerning muscle-based gene therapy.

Regarding Rubanyi, cited by the Examiner in the paragraph bridging pages 5-6 of the Action, it is noted in the abstract that gene therapy prerequisites for success include therapeutically suitable genes, appropriate gene delivery systems, and proof or principle of efficacy and safety in appropriate clinical models. The instant specification establishes each of these factors, and the methods of the present invention have found application in the treatment of disease. The examples provided in the specification can be applied in providing guidance to one of ordinary skill in the art, particularly in view of the state of the art pertaining to muscle-based gene therapy, to apply the claimed invention to increase serum levels of a protein to treat a disease. Thus, while it may be possible that some experimentation may be required to practice the claimed invention in some embodiments, no sufficient evidence has been set forth by the Examiner to show that any such experimentation would be undue experimentation. See *MPEP* §2164.06.

As further evidence that the claimed methods can be used in gene therapy applications to produce a therapeutic effect, Applicant previously submitted the following Exhibits which support that the specification as written supports enablement of the claimed invention:

- Wang and Herzog, "AAV-Mediated Gene Transfer for Treatment of Hemophilia," Current Gene Therapy, 2005, 5, 349-360 (Exhibit 2 of response to Office Action dated Feb. 13, 2007). This report presents an overview of the state of the art pertaining to AAV-mediated factor IX gene transfer to skeletal muscle of animals and humans. The Abstract indicates that gene transfer of coagulation factor VII and IX to skeletal muscle and liver of murine and canine models of hemophilia A and B have resulted in "sustained systemic expression and, in several studies, in complete cure of the bleeding disorder." Abstract. This reference evidences that the claimed processes have been successfully applied in factor IX gene transfer, and that no undue experimentation is required to practice the claimed methods.

- Kay *et al.*, "Evidence for gene transfer and expression of Factor IX in haemophilia B patients treated with an AAV vector. Nat. Genet. (2000), 24:257-261 (Exhibit 3 of response to Office Action dated Feb. 13, 2007).

- Manno *et al.*, "AAV-mediated Factor IX gene transfer to skeletal muscle in patients with severe hemophilia B." Blood (2003) 101:2963-2972 (Exhibit 4 of response to Office Action dated Feb. 13, 2007).

These references are not cited to show the state of the art at the time the present application was filed, but are cited to demonstrate that the present specification as written is

enabling for the scope of the claims, and to demonstrate that the claimed methods can in fact be used in gene therapy applications. These references do not establish that undue experimentation would be required to practice the claimed methods. The Examiner writes that "absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect, the claims directed to methods for gene therapy are not enabled by the disclosure." Office Action, page 5. Applicant disagrees, again directing the Examiner to the above references which further support that the specification as written enables the claims for their full scope. While there may have been some experimentation involved, there is nothing to suggest that any such experimentation was undue.

Regarding new claims 38-51, their either depend from claim 5 or claim 30, which for the reasons discussed above are sufficiently enabled by the present specification.

In view of the foregoing, each of the pending claims is enabled by the instant specification. Regarding new claim 37, it depends from claim 1, which for the reasons discussed above is enabled by the instant specification. Therefore, it is respectfully requested that the enablement rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

C. The Rejections Under 35 U.S.C. §102 Are Moot

1. The Rejections Under §102(b) Based on Tripathy *et al.* Are Moot

Claims 1, 4, and 6-10 are rejected under 35 U.S.C. §102(b) as being anticipated by Tripathy *et al.* (1994, PNAS 91:11557-11561, cited in IDS; hereinafter "Tripathy"). Applicant respectfully traverses.

Without conceding that the claims as originally written were anticipated by Tripathy, Applicant notes that independent claim 1 has been amended to recite the limitations of claim 3, a

claim which was not included in this rejection and thus considered by the Examiner to not be anticipated by Tripathy. Further, claims 4 and 6-10 are not anticipated by Tripathy because they each depend from claim 1. In view of the foregoing, the rejection of claims 1, 4, and 6-10 under 35 U.S.C. §102(b) as being anticipated by Tripathy is moot.

2. The Rejections Under §102(b) Based on Dhawan *et al.* Are Moot

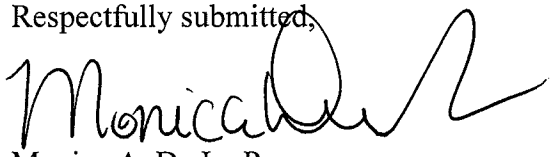
Claims 24, 28, 29, 31, 32, 34, 35, and 36 are rejected under 35 U.S.C. §102(b) as being anticipated by Dhawan *et al.* (1991, Science 254:1509-1512, cited in IDS; hereinafter "Dhawan"). Applicant respectfully traverses.

Without conceding that the claims as originally written were anticipated by Dhawan, Applicant notes that independent claim 24 has been amended to recite the limitations of claim 26, a claim which was not included in this rejection and thus considered by the Examiner to not be anticipated by Dhawan. Further, claims 28, 29, 31, 32, 24, 25, and 26 are not anticipated by Dhawan because they each depend from claim 24. In view of the foregoing, the rejection of claims 24, 28, 29, 31, 32, 34, 35, and 36 under 35 U.S.C. §102(b) as being anticipated by Dhawan is moot.

D. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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